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PERSPECTIVES

Back to the salt mines – endothelial dysfunction in hypertension and compensatory role of endothelium-derived hyperpolarizing factor (EDHF)

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Evidence continues to accumulate on the importance of EDHF in vascular homeostasis (Feletou & Vanhoutte, 2001; Golding *et al.* 2002; Selemidis & Cocks, 2002). A number of physical and chemical stimuli can activate endothelial cells to produce and release vasodilator substances including nitric oxide and prostacyclin. In some blood vessels activation of the endothelium causes hyperpolarization of both endothelium and underlying smooth muscle cells, leading to vasodilatation. The chemical nature of EDHF as well as the contribution of direct transfer of hyperpolarizing current from endothelial cells to smooth muscle cells has been an object of intense investigation ever since the original observation of endothelium-dependent hyperpolarization by Feletou and Vanhoutte in 1988. Potassium ions, cytochrome-P450-derived epoxyeicosatrienoic acids (EETs), and hydrogen peroxide have been proposed as possible EDHFs (Feletou & Vanhoutte, 2001). Spreading of hyperpolarizing current via myoendothelial junctions is another key mechanism of endothelium-dependent hyperpolarization (Feletou & Vanhoutte, 2001). Despite remaining uncertainties regarding the exact nature of EDHF, consensus has been reached that initiation of hyperpolarization is dependent on activation of Ca^{2+}-sensitive K^+ (K_{Ca}) channels in endothelial cells. Apamin and charybdotoxin selectively inhibit K_{Ca} channels. These compounds are valuable pharmacological tools needed for the characterization of the role of EDHF in control of vascular function.

The concept of vascular endothelial dysfunction emerged from recognition of the critical role endothelium plays in the regulation of vasomotor function, inflammation, blood coagulation, and angiogenesis. Dysfunctional endothelium favours vasoconstriction, smooth muscle cell proliferation, platelet aggregation, and white blood cell adhesion, and may impair angiogenesis. Numerous studies suggest that loss of the biological activity of nitric oxide and/or its biosynthesis is the central mechanism responsible for endothelial dysfunction (Katusic, 2001). The exact mechanisms responsible for endothelial dysfunction in arteries exposed to chronic hypertension are not completely understood, but may involve chemical antagonism between superoxide anions and nitric oxide and functional antagonism of nitric oxide-mediated vasodilatation due to release of endothelium-derived contracting factor(s) (Katusic & Shepherd, 1991; Vanhoutte, 1996).

The study by Sofola *et al.* (2002), reported in this issue of *The Journal of Phsyiology*, provides evidence that in hypertension induced by a high salt diet, EDHF may compensate for the loss of nitric oxide and preserve endothelium-dependent relaxations in response to acetylcholine in mesenteric resistance arteries. This observation supports the concept that EDHF may serve as an important compensatory mechanism in arteries exposed to hypertension. *More importantly, this observation illustrates that, in diseased arteries, 'normal' endothelium-dependent relaxations in response to acetylcholine should not be interpreted as if there is no alteration in endothelial function.* Analysis of the mechanism underlying endothelium-dependent relaxation is critical and can unmask endothelial dysfunction due to loss of nitric oxide.

Increased vascular resistance is certainly one of the most important mechanisms responsible for the pathogenesis of hypertension. Emerging evidence strongly suggests that the relative contribution of EDHF to endothelial control of vasomotor function increases as the diameter of the blood vessel decreases (Golding *et al.* 2002). Although the exact role of EDHF in the pathogenesis of hypertension is not completely understood, it appears that localization of EDHF in small resistance arteries is an important mechanism designed to maintain normal vascular resistance. In contrast to nitric oxide, EDHF is not inactivated by oxidative stress. Nitric oxide acts locally whereas EDHF-induced vasodilatation may spread to remote segments of the arterial wall (Selemidis & Cocks, 2002). These characteristics may explain why EDHF can function as a back-up mechanism in vascular diseases associated with oxidative stress and subsequent loss of local homeostatic control mediated by nitric oxide.

As acknowledged in the Discussion of the present study by Sofola and colleagues (2002), in mesenteric arteries acetylcholine is not the physiological stimulus for the release of nitric oxide or EDHF. It would certainly be interesting to know whether shear stress-induced vasodilatation is affected by hypertension and whether EDHF may play the same compensatory role as it does in endothelium-dependent relaxations in response to acetylcholine. Furthermore, the precise mechanism responsible for the compensatory effect of EDHF in salt-induced hypertension is unclear. Is it due to up-regulation of EDHF formation and/or release? Does hypertension change reactivity of smooth muscle cells to EDHF? Is there any change in the conductivity of hyperpolarization? Does a high salt diet affect the expression and function of the proteins involved in the formation of gap junctions and the propagation of hyperpolarization? Obviously these questions remain to be answered in future studies. A better understanding of EDHF and its ability to act as a compensatory mechanism may provide the basis for development of new therapeutic approaches to vascular endothelial dysfunction.

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